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(54) SUBSTITUTED CYCLOHEXANAMIDES, THEIR PREPARATION AND USE AS COLD RECEPTOR STIMULANTS

(71) We, WILKINSON SWORD LIMITED, a British Company, of Sword Works, Southfield Road, London, W.4, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to ingestible, topical and other compositions having a physiological cooling effect on the skin and on the mucous membranes of the body, particularly the nose, mouth, throat and gastrointestinal tract.

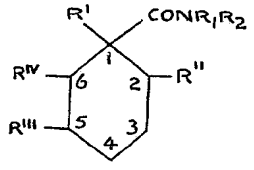
Menthol is well known for its physiological cooling effect on the skin and mucous membranes of the mouth and has been extensively used as a flavouring agent (menthol being a major constituent of oil of peppermint) in foodstuffs, beverages, dentifrices, mouthwashes, etc. and as a component in a wide range of toiletries, liniments and lotions for topical application. Menthol is also a well known tobacco additive for producing a "cool" sensation in the mouth when smoking. Carvomenthol has also been reported as having a physiological cooling effect and so also have N,N - dimethyl - 2 - ethyl butanamide and N,N - diethyl - 2 - ethyl butanamide, see French Patent No. 1,572,332.

It is well established that the "cooling" effect of methanol is a physiological effect due to the direct action of menthol on the nerve endings of the human body responsible for the detection of hot or cold and is not due to latent heat of evaporation. It is believed that the menthol acts as a direct stimulus on the cold receptors at the nerve endings which in turn stimulate the central nervous system.

Although menthol is well established as a physiological coolant its use, in some compositions, is circumscribed by its strong minty odour and its relative volatility.

The present invention is based on the discovery that certain other organic compounds have a physiological cooling effect similar to that obtained with methanol, but do not have the strong minty odour. In many cases the compounds have little or no odour at all. Such compounds therefore find utility as additives in a wide range of ingestible and topical compositions.

The compounds having a physiological cooling effect and utilized in accordance with the present invention are substituted cyclohexanamides of the formula



where

R', R'', R''' and R'' are each hydrogen or C_1—C_5 alkyl and together provide a total of from 1—8 carbon atoms, it being provided that at least two of R', R'' and R'''

and R'^{v} are hydrogen and that, when R' and R'^{v} are both hydrogen and R''' is methyl, then R'' is methyl, ethyl, n-propyl or straight or branched chain butyl or amyl;

R_1 and R_2, when taken separately, each represent hydrogen, C_1—C_5 alkyl or C_1—C_8 hydroxylalkyl and together provide a total of no more than 8 carbon atoms with the proviso that when R_1 is hydrogen R_2 may also be alkylcarboxyalkyl of up to 6 carbon atoms; and

R_1 and R_2, when taken together, represent an alkylene group of up to 6 carbon atoms the end of which group are attached to the amide nitrogen atom thereby to form a nitrogen heterocycle, the carbon atom chain of which may optionally be interrupted by oxygen.

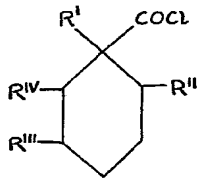
In accordance with one aspect of this invention, therefore, there are provided manufactured products for application to or consumption by the human body comprising a physiologically active ingredient capable of stimulating the cold receptors of the nervous system of the body and a carrier therefor, said carrier constituting or providing a vehicle by means of which said ingredient may be brought into contact with the skin or other surface tissue of the body upon use of the said product, said carrier comprising a manufactured article or preparation into which the said ingredient is incorporated by admixture or impregnation and being other than a liquid or mixture of liquids which serve merely as solvent for the said ingredient and which contain no other ingredient, wherein said physiologically active ingredient is a cyclohexanamide of the formula defined above. In a second aspect, there is provided a method of stimulating the cold receptors of the nervous system of the human body, other than as part of a medical treatment, which comprises applying to the skin, or other surface tissue of the body, a cyclohexanamide of the formula defined above.

The preferred cyclohexanamides used in the products and method of this invention are cyclohexanamides having either one or two nuclear alkyl substituents with the nuclear alkyl substituent in the case of the mono-nuclear substituted compounds being either in the 1- or the 2-position and the second being either in the 5- or the 6-position. Especially preferred are tertiary compounds, i.e. where R' is alkyl. Generally it is preferred that one alkyl group, preferably R', is a branched chain group with branching in an alpha or beta position relative to the ring.

Also preferred are monosubstituted amides, i.e. where one of R_1 and R_2 is hydrogen, and disubstituted amides where R_1 and R_2 are methyl or ethyl.

The substituted cyclohexanamides of the above formual exhibit both geometric and optical isomerism and the present invention contemplates using the compounds in an isomerically pure state i.e. consisting of one geometric or optical isomer, as well as in isomer mixtures. In most cases the compounds will be used as an isomer mixture but with certain compounds there may be a difference in cooling effect as between isomers, for example, as between d- and l-forms, and in such cases one or other isomeric form may be preferred.

The amides used in this invention may readily be prepared by conventional techniques, for example, by reaction of an acid chloride of the formula



with an amine of the formula HNR_1R_2 in the presence of a hydrogen chloride acceptor. Such reactions are entirely conventional and the procedures involved will readily be understood by persons skilled in the art.

Typical amides usable according to the invention are indicated in the following table, together with an indication of their relative activity, i.e. the degree of cooling produced by a given quantity of the compound; the more stars the greater the activity.

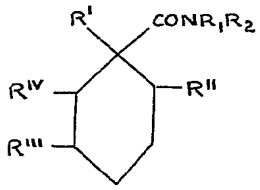
TABLE

R′	R′′	R′′′	R′V	R_1	R_2	Activity
iso-C_3H_7-	H	H	H	H	C_2H_5-	*****
,,	,,	,,	,,	CH_3-	CH_3-	*****
,,	,,	,,	,,	CH_2-CH_2 | CH_2-CH_2		*****
n-C_3H_7	,,	,,	,,	CH_3-	CH_3-	*****
iso-C_3H_7-	CH_3-	,,	,,	H	C_2H_5-	*****
sec-C_4H_9-	H	,,	,,	,,	,,	*****
iso-C_4H_9-	CH_3-	,,	,,	,,	,,	*****
,,	,,	,,	,,	,,	$HOCH_2C(CH_3)_2$-	*****
,,	,,	,,	,,	CH_3-	CH_3-	*****
C_2H_5-	C_2H_5-	,,	,,	H	C_2H_5	*****
n-C_3H_7-	H	,,	,,	,,	n-C_4H_9-	****
C_2H_5-	CH_3-	,,	,,	,,	C_2H_5-	****
,,	,,	,,	,,	,,	$HOCH_2C(CH_3)_2$-	****
,,	,,	,,	,,	CH_3-	CH_3-	****
,,	C_2H_5	,,	,,	H	,,	****
H	,,	,,	,,	,,	C_2H_5-	****
sec-C_4H_9-	H	,,	,,	CH_3-	CH_3-	****
CH_3-	H	,,	,,	H	C_2H_5-	***
n-C_3H_7-	,,	,,	,,	,,	,,	***
,,	,,	,,	,,	,,	-$CH_2CH_2OCH_2CH_2$-	***
H	n-C_4H_9	,,	,,	H	C_2H_5-	***
C_2H_5-	C_2H_5-	,,	,,	,,	$HOCH_2C(CH_3)_2$-	***
CH_3-	H	,,	,,	,,	n-C_4H_9	**
H	CH_3-	,,	,,	,,	C_2H_5-	**
,,	C_2H_5-	,,	,,	,,	$C_2H_5OOCCH_2$-	**
,,	,,	,,	,,	,,	$HOCH_2C(CH_3)_2$-	**
sec-C_4H_9-	H	,,	,,	,,	H	**
iso-C_3H_7-	,,	,,	,,	,,	,,	**
n-C_3H_7	,,	,,	,,	,,	,,	**

TABLE (continued)

R′	R″	R‴	R′V	R_1	R_2	Activity
H	n-C_4H_9-	H	H	H	$C_2H_5OOCCH_2$-	*
,,	CH_3-	CH_3-	,,	,,	C_2H_5-	*
,,	,,	,,	CH_3-	CH_3-	CH_3-	*

Certain of the compounds used in accordance with the present invention are novel compounds and as such represent a further aspect of the present invention. The novel compounds are mono- and di-substituted amides of the formula



where R′, R″, R‴ and R′ᵛ are as defined above except that, together, they provide a total of from 2—8 carbon atoms, R_1 when taken separately is hydrogen, C_1—C_5 alkyl or C_1—C_8 hydroxyalkyl, R_2 when taken separately, represents C_1—C_5 alkyl or C_1—C_8 hydroxyalkyl and together with R_1 provides a total of up to 8 carbon atoms, with the proviso that when R_1 is hydrogen, R_2 may also be alkylcarboxylalkyl of up to 6 carbon atoms; and when taken together R_1 and R_2 represent an alkylene group of up to 6 carbon atoms, the opposite ends of which group are attached to the amide nitrogen atom to form a nitrogen heterocycle, the carbon atom chain of which may be interrupted by oxygen.

The compounds of the above formulae find utility in a wide variety of manufactured products for consumption by or application to the human body. Broadly speaking, these compositions can be divided into comestible and topical compositions, both terms being taken in their broadest possible sense. Thus comestible is to be taken as including not only foodstuffs and beverages taken into the mouth and swallowed, but also other orally ingested compositions taken for reasons other than their nutritional value, e.g. indigestion tablets, antacid preparations and laxatives. Comestible compositions are also to be taken to include edible compositions taken by mouth, but not necessarily swallowed, e.g. chewing gum. Topical compositions are to be taken as including not only compositions, for example, perfumes, powders, lotions, liniments, oils and ointments applied to the external surfaces of the human body, whether for medical or other reasons, but also compositions applied to, or which, in normal usage, come in contact with, internal mucous membranes of the body, for example those of the nose, mouth, or throat, whether by direct or indirect application or inhalation, and thus include nasal and throat sprays, dentifrice, mouthwash and gargle compositions. Also included within the present invention are toilet articles, for example cleansing tissues and toothpicks impregnated or coated with the active cooling compound.

A further class of manufactured products included within the scope of this invention are tobacco and associated articles e.g. pipe and cigarette filters, especially filter tips for cigarettes.

The manufactured products of this invention will contain an amount of the active cooling compound sufficient to stimulate the cold receptors in the areas of the skin or mucous membrane with which the products come into contact and thereby promote the desired cold sensation. As the degree and longevity of cooling sensation varies from compound to compound the quantity of stimulant used in each product will vary widely. As a guide, it may be said that, with the more active compounds, a significant cooling sensation, which, in some cases, may persist for several hours, is achieved upon application to the skin of as little as 0.05 ml of a 1.0% weight percent solution of the active ingredient in ethanol. For the less active compounds a significant cooling effect is achieved only with more concentrated solutions, e.g. 5% by weight or more of the active ingredient. It must also be admitted that such skin tests are somewhat subjective, some individuals experiencing a greater or lesser cooling sensation than others when subjected to the same test.

In formulating the product of this invention the active cooling compound will usually be incorporated into a carrier which may be completely inert or which may be or contain other active ingredients. A wide variety of carriers will be suitable, depending upon the end use of the composition, such carriers including solids, liquids, emulsions, foams and gels. Typical carriers for the active cooling compound include aqueous or alcoholic solu-

tions; oils and fats, for example hydrocarbon oils, fatty acid esters, long chain alcohols and silicone oils; finely divided solids for example starch or talc; cellulosic materials for example paper tissue; tobacco; low-boiling hydrocarbons and halohydrocarbons used as aerosol propellants; gums and natural or synthetic resins.

In most products according to the invention the carrier will be or contain as an adjuvant one or more of the following: an antacid, antiseptic or analgesic, a flavourant, colourant, or odourant, or a surfactant.

The following illustrate the range of manufactured products into which the active cooling compounds can be incorporated:

1. Edible or potable compositions including alcoholic and non-alcoholic beverages, confectionery, chewing gum, cachous, ice cream; jellies;
2. Toiletries including after shave lotions, shaving soaps, creams and foams, toilet water, deodorants and antiperspirants, " solid colognes ", toilet soaps, bath oils and salts, shampoos, hair oils, talcum powders, face creams, hand creams, sunburn lotions, cleansing tissues, dentifrices, toothpicks, mouthwashes, hair tonics, eyedrops.
3. Medicaments including antiseptic ointments, pile ointments, liniments, lotions, decongestants, counter-irritants, cough mixtures, throat lozenges, antacid and indigestion preparations, oral analgesics;
4. Tobacco preparations including cigars, cigarettes, pipe tobacco, chewing tobacco and snuff; tobacco filters, especially filter tips for cigarettes.
5. Miscellaneous compositions for example water soluble adhesive compositions for envelopes, postage stamps and adhesive labels.

Particular preparations according to the invention are discussed in more detail below.

Edible and Potable Compositions.

The edible and potable compositions of this invention will contain the active cooling compound in combination with an edible carrier and usually a flavouring or colouring agent. The particular effect of the cooling compounds is to create a cool or fresh sensation in the mouth, and in some cases, even in the stomach, and therefore the compounds find particular utility in sugar-based confectionery for example chocolate, boiled sweets and candy, in ice cream and jellies and in chewing gum. The formulation of such confections will be by ordinary techniques and according to conventional recipes and as such forms no part of this invention. The active compound will be added to the recipe at a convenient point and in amount sufficient to produce the desired cooling effect in the final product. As already indicated, the amount will vary depending upon the particular compound, the degree of cooling effect desired and the strength of other flavourants in the recipe. For general guidance, however, amounts in the range 0.1 to 5.0% by weight based on the total composition will be found suitable.

Similar considerations apply to the formulation of beverages. Generally speaking the compounds will find most utility in soft drinks e.g. fruit squashes, lemonade and cola, but may also be used in alcoholic beverages. The amount of compound used will generally be in the range 0.1 to 2.5% by weight based on the total composition.

Toiletries

Because of the cooling sensation imparted to the skin, a major utility of the cooling toilet preparations and toilet articles. The particular preparations discussed below are to be taken as exemplary.

A major utility will be in after shave lotions and toilet water, where the compound will be used in alcoholic or aqueous alcoholic solution, such solutions usually also containing a perfume or mild antiseptic or both. The amount of compound added to the formulation will usually be in the range 0.1 to 10% by weight based on the total composition.

Another field of utility will be in soaps, shampoos and bath oils where the compound will be used in combination with an oil or fat or a natural or synthetic surfactant e.g. a fatty acid salt or a lauroylsulphate salt, the composition usually also containing an essential oil or perfume. The range of soap compositions will include soaps of all kinds e.g. toilet soaps, shaving soaps and shaving foams. Usually the compound will be added to the formulation in an amount of from Q1 to 10% by weight.

A further class of toilet compositions into which the compounds may be incorporated includes cosmetic creams and emollients, such creams and emollients usually comprising a base emulsion and optionally a range of ingredients for example wax, preservative, perfume, antiseptics, astringents and pigments. Also included within this class are lipstick compositions such compositions usually comprising an oil and wax base into which the compound can be incorporated along with the conventional ingredients i.e. pigments and perfumes. Once again the formulation of such compositions, apart from the incorporation of the cooling compound, usually in an amount of from 0.05 to 10% by weight, is conventional.

Compositions for oral hygiene containing the cooling compounds include mouthwash, gargle and dentifrice compositions. The first

two may be considered together and will usually comprise an aqueous, alcoholic, or aqueous-alcoholic solution of an antiseptic often coloured or flavoured for palatability, to which the coolant is added in an amount of from 0.1 to 1.0% by weight.

Dentifrice compositions may be of the solid block, powder, paste or liquid type and will usually comprise a finely divided abrasive or polishing material, e.g. precipitated chalk, silica, magnesium silicate or aluminium hydroxide, and a detergent or foaming agent. Optional ingredients which also be included are flavouring agents and colourants, antiseptics, lubricants, thickeners, emulsifiers or plasticizers. The amount of coolant added in such compositions will generally be from 0.1 to 5.0% by weight based on the total composition.

Medicaments

Because of their cooling effect on the skin and on the mucous membranes of the mouth, throat and nose of the gastrointestinal tract the cooling compounds may be used in a variety of oral medicines, nasal and throat sprays, and topical compositions, particularly where a counter-irritant is required. In particular the coolants may be formulated into antacid and indigestion remedies, in particular those based on sodium bicarbonate, magnesium oxide, calcium or magnesium carbonate, aluminium or magnesium hydroxide or magnesium trisilicate. In such composition the coolant will usually be added in an amount of from 0.1 to 2.0% by weight.

The coolants may also be included in oral analgestic compositions e.g. when acetylsalicylic acid or its salts, and in nasal decongestants e.g. those containing ephedrine.

Tobacco Preparations.

The coolants of this invention may be incorporated directly into tobacco to give a cool effect when smoking but without the attendant strong and characteristic odour which is associated with mentholated tobacco and cigarettes. Such compositions also have considerable storage stability, which is in contrast with mentholated products. However, a more advantageous utilisation of the coolants of this invention is in pipe or cigarette filters, in particular, filter tipped cigarettes. The pad of filter material, which may be of any of the well known types, e.g. cellulose acetate, paper, cotton α-cellulose or asbestos fiber, is simply impregnated with an alcoholic solution of the coolant and dried to deposit the coolant in the filter pad. The effect is to give a pleasant cool sensation in the mouth when the cigarette is smoked. As little as 0.1 mg. of the coolant is effective.

Compositions of this invention are illustrated by the following Examples.

EXAMPLE I.

After Shave Lotion

An after shave lotion was prepared according to the following recipe by dissolution of the ingredients in the liquid and cooling and filtering:

Denatured Ethanol	75%
Diethylphthalate	1.0%
Propyllene Glycol	1.0%
Lactic Acid	1.0%
Perfume	3.0%
Water	to 100%

Into the base lotion was added 1.0% by weight based on the total composition of N - ethyl - 2 - methyl - 1 isopropylcyclohexanamide.

When the final lotion is applied to the face a clearly noticeable cooling effect becomes apparent after a short interval of time.

EXAMPLE II.

Eye Lotion

An eye lotion was prepared containing the following ingredients:

Witch Hazel	12.95%
Boric Acid	2.00%
Sodium Borate	0.50%
Allantoin	0.05%
Salicylic Acid	0.025%
Chlorobutol	0.02%
Zinc Sulphate	0.004%
Water	to 100%

To the formulation was added 0.01%, based on the total composition, of N,2-diethylcyclohexanamide. When used to bathe the eyes a cool fresh sensation is apparent on the eyeball and eyelids.

EXAMPLE III.

Toothpaste

The following ingredients were mixed in a blender:

Dicalcium Phosphate	48.0%
Sodium lauryl sulphate	2.5%
Glycerol	24.8%
Sodium carboxymethyl cellulose	2.0%
Citrus flavourant	1.0%
Sodium saccharin	0.5%
Water	to 100%

Shortly before completion of the blending operation 1% by weight of N,N - dimethyl-1 - isopropylcyclohexanamide was added to the blender.

When applied as a toothpaste, a cooling effect is noticed in the mouth.

EXAMPLE IV.

Soft-Sweet

Water was added to icing sugar at 40° C. to form a stiff paste. 0.5% of N - ethyl - 1-*n* - propylcyclohexanamide was then stirred into the paste and the mixture allowed to set. A soft sweet mass resulted having the characteristic cooling effect in the mouth of peppermint but without the minty flavour or odour.

EXAMPLE V.

Cigarette Tobacco

A proprietary brand of cigarette tobacco was impregnated with N - ethyl - 1 - isopropylcyclohexanamide and was rolled into cigarettes each containing approximately 0.001 gm. of active compound. Smoking the impregnated cigarettes produced a cool effect in the mouth characteristic of mentholated cigarettes but without any attendant odour other than that normally associated with tobacco.

A similar effect is noticed when smoking a proprietary brand of tipped cigarette, the coolant being used to impregnate the filter tip rather than the tobacco.

EXAMPLE VI.

Antiseptic Ointment

An ointment was prepared acocrding to the following formulation:

Cetyltrimethyl ammonium bromide	4.0%
Cetyl Alcohol	6.0%
Stearyl Alcohol	6.0%
White Paraffin	14.0%
Mineral Oil	21.0%
Water	to 100%

The ingredients were mixed, warmed to 40° C. and emulsified in a high speed blender. Added to the mixture during blending was 3.0% N - (1,1 - dimethyl - 2 - hydroxyethyl) - 1 - isobutyl - 2 - methylcyclohexanamide.

The final ointment when applied to the skin gave rise to a marked cooling effect.

EXAMPLE VII.

Aerosol Shaving Soap

An aerosol shaving soap composition was formulated according to the following recipe:

Stearic acid	6.3%
Lauric acid	2.7%
Triethanolamine	4.6%
Sodium carboxymethyl cellulose	0.1%
Sorbitol	5.0%
Perfume	0.4%
Water	to 100%

The composition was prepared by fusing the acids in water, adding the triethanolamine, cooling and adding the other constituents. To the mixture was then added 2.0%, based on the total composition of N,2-diethyl cyclohexanamide. The composition was then packaged in an aerosol dispenser under pressure of a butane propellant.

When used in shaving a fresh cool sensation was distinctly noticeable on the face.

EXAMPLE VIII.

Toilet Water

A toilet water was prepared according to the following recipe:

Denatured ethanol	75.0%
Perfume	5.0%
Water	to 100%

To the recipe was added 3.0% based on the total composition, of N,N,2 - trimethyl - 1-isobutylcyclohexanamide.

As with the after shave lotion, a cooling effect was clearly noticeable on the skin well after the termination of any cooling effect attributable to the evaporation of the alcoholic carrier.

EXAMPLE IX.

Deodorant Composition

A deodorant composition suitable for formulation and dispensing as an aerosol under pressure of a suitable propellant was formulated according to the following recipe:

Denatured ethanol	96.9%
Hexachlorophene	2.0%
Isopropyl myristate	1.0%
Perfume	0.1%

To the composition was added 2.5% by weight of N - (2 - hydroxy - 1,1 - dimethyl - ethyl)-1 - ethyl - 2 - methyl cyclohexanamide. Application of the final composition gave rise to a definite cooling sensation on the skin.

EXAMPLE X.

Hair Shampoo

Sodium lauryl ether sulphate, 10 g, was dispensed in 90 g. water in a high speed mill. To the dispersion was added 3.0% by weight of N - methyl - 1,2 - diethyl cyclohexanamide. When the hair is washed using the shampoo a fresh, cool sensation is noticed on the scalp.

EXAMPLE XI.

Solid Cologne

A solid cologne was formulated according to the following recipe:

Denatured ethanol	74.5%
Propylene glycol	3.0%
Sodium stearate	5.0%
Perfume	5.0%
Water	to 100%

The sodium stearate was dissolved by stirring in a warm mixture of the ethanol, propylene glycol and water. To the solution was added the perfume and 2.0% of N - ethyl - 1 - sec.butyl cyclohexanamide and the mixture then allowed to solidify into a waxy cake. When applied to the forehead a distinct cooling effect is noticeable.

EXAMPLE XII.

Mouthwash

A concentrated mouthwash composition was prepared according to the following recipe:

Ethanol	3.0%
Borax	2.0%
Sodium bicarbonate	1.0%
Glycerol	10.0%
Flavourant	0.4%
Thymol	0.03%
Water	to 100%

To the composition was added 0.1% of N-ethyl - 1 - isopropyl - 2 - methyl cyclohexanamide.

When diluted with approximately 10 times its own volume of water and used to rinse the mouth a cooling effect is obtained in the mouth.

EXAMPLE XIII.

Toothpicks

The tip of a wooden toothpick was impregnated with an alcoholic solution containing N-ethyl - 1 - methylcyclohexanamide in sufficient amount to deposit on the toothpick 0.10 mg. of the compound. The impregnated toothpick was then dried. When placed on the tongue there is no detectable taste, however, a distinct cooling effect is noticeable after a short period of time.

EXAMPLE XIV.

Soft Drink

A soft drink concentrate was prepared from the following recipe:

Pure orange juice	60%
Sucrose	10%
Saccharin	0.2%
Orange flavouring	0.1%
Citric acid	0.2%
Sulphur dioxide	trace amount
Water	to 100%

To the concentrate was added 0.10% of N-n - butyl - 1 - n - propyl cyclohexanamide.

The concentrate was diluted with water and tasted. An orange flavour having a pleasantly cool after-effect was obtained.

EXAMPLE XV.

Boiled Sweet

99.5% sucrose and 0.5% citric acid were carefully fused together in the presence of a trace of water. Just before casting the melt onto a chilled plate 0.5% of N - ethyl - 1-isopropyl cyclohexanamide was rapidly stirred in. The melt was then cast. A boiled sweet resulted having a marked cooling effect on the mouth.

EXAMPLE XVI.

Indigestion Tablet

The following ingredients were ground together:

Magnesium carbonate	49.5%
Sorbitol	49.4%
Saccharin	0.1%
Talc	1.0%

Added to the mixture during grinding was 0.10% of N,N,2 - trimethyl - 1 - ethylcyclohexanamide. After mixing the mixture was pressed into 0.5 g. tablets.

Taken by mouth and swallowed the tablets produced after a short interval of time a noticeable cooling effect in the stomach.

EXAMPLE XVII.

Cleansing Tissue

A cleansing liquid was prepared having the formulation:

Triethanolamine Lauryl Sulphate	1.0%
Glycerol	2.0%
Perfume	.95%
Water	to 100%

To this liquid was added 2.0% of N,1,2-triethyl cyclohexanamide. A paper tissue was then soaked in the liquid.

When the impregnated tissue was used to wipe the skin a fresh cool sensation developed on the skin after a short interval.

The above Examples illustrate the range of compounds and the range of compositions included within the present invention. However, they are not to be taken as limiting the scope of the invention in any way. Other compounds within the general formula will be equally suitable for use in the compositions of Examples I—XVII and the physiological cooling effect obtained with the compounds of the invention will recommend their use in a wide variety of other compositions where the cooling effect will be of value.

The novel compounds of this invention are illustrated by the following Examples. All temperatures are given in degrees Centigrade. The cyclohexanecarboxylic acids used as starting materials were prepared either by carbonation of Grignard reagents or by hydrolysis of alkylcyclohexyl cyanides according to known techniques.

EXAMPLE XVIII.

PREPARATION OF N - ETHYL - 1 - ISOPROPYLCYCLOHEXANAMIDE

1-isopropylcyclohexanoyl chloride was prepared from 1-isopropylcyclohexanoic acid and thionyl chloride. A solution of this acid chloride (2.6 g) in ether (25 ml) was added dropwise to a stirred solution of ethylamine (5 ml of a 70% solution in water) in ether (100 ml). After 2 hours the ethereal solution was washed with dilute hydrochloric acid and water, dried ($MgSO_4$) and concentrated to give a white solid. This was recrystallised from petroleum ether (bp. 40—60° C.) to give N-ethyl - 1 - isopropylcyclohexanamide, mp. 101—2°.

Analysis:
Found
C: 73.5; H: 11.9; N: 7.2
Calculated
C: 73.2; H: 11.7; N: 7.1%

EXAMPLE XIX.

PREPARATION OF N - n - BUTYL - 1-n - PROPYLCYCLOHEXANAMIDE

1 - n - propylcyclohexanoyl chloride (bp. 118—122°/16mm) was prepared in the usual way from 1 - n - propylcyclohexanoic acid and thionyl chloride. A solution of this acid chloride (2.0 g) in ether (20 ml) was added dropwise to a stirred solution of n-butylamine (3.0 g) in ether (100 ml). After 3 hours the ethereal solution was washed with dilute hydrochloric acid and water, dried ($MgSO_4$), and concentrated to give a colourless syrup. Distillation gave N - n - butyl - 1 - n - propylcyclohexanamide, bp. 116—8°/1mm.

Analysis:
Found
C: 74.8; H: 12.1; N: 6.3
Calculated
C: 74.7; H: 12.0; N, 6.2%

EXAMPLE XX.

PREPARATION OF N,N - DIMETHYL-1 - n - PROPYLCYCLOHEXANAMIDE

The procedure of Example XIX was repeated but using dimethylamine in place of n-butylamine, N,N - dimethyl - 1 - n - propylcyclohexanamide was obtained as a colourless liquid, bp. 63—66°/0.01 mm.

Analysis:
Found
C: 73.7; H: 11.7; N: 7.3
Calculated
C: 73.0; H: 11.7; N: 7.1%

EXAMPLE XXI.

PREPARATION OF N - (1 - n - PROPYLCYCLOHEXANOYL)MORPHOLINE

The procedure of Example XIX was repeated but using morpholine in place of n-butylamine. N - (1 - n - propylcyclohexanoyl)-morpholine was obtained as a colourless syrup, bp. 105—114°/0.01 mm.

Analysis:
Found
C: 70.1; H: 10.9; N: 5.7
Calculated
C: 70.5; H: 10.5; N: 5.9%

EXAMPLE XXII.

PREPARATION OF N - (1,1 - DIMETHYL - 2 - HYDROXYETHYL)-1 - ETHYL - 2 - METHYLCYCLOHEXANAMIDE

1 - ethyl - 2 - methylcyclohexanoyl chloride (bp. 108—114°/15 mm) was prepared in the usual way. A solution of this acid chloride (1.0 g) in ether (20 ml) was added to a stirred solution of 2 - amino - 2 - methylpropan - 1 ol (1.0 g) in ether (100 ml). After 17 hours the product was isolated as in Example XVIII. Distillation gave N - (1,1 - dimethyl - 2 - hydroxyethyl) - 1 - ethyl - 2-methylcyclohexanamide, bp. 136—143°/1.0 mm, as a colourless liquid which slowly solidified.

Analysis:
Found
C: 69.1; H: 11.3; N: 5.7
Calculated
C: 69.7; H: 11.2; N: 5.8%

EXAMPLE XXIII.

PREPARATION OF N,N,2-TRIMETHYL-1 - ISOBUTYLCYCLOHEXANAMIDE

1 - isobutyl - 2 - methylcyclohexanoyl chloride (bp. 124—126.5°/10 mm) was prepared in the usual way. A solution of this acid chloride in ether was treated with dimethylamine as in Example XX. After work up, distillation of the residue gave N,N,2-trimethyl - 1 - isobutylcyclohexanamide, bp. 103—107°/0.9 mm.

Analysis:
Found
C: 74.0; H: 12.2; N: 6.3
Calculated
C: 74.6; H: 12.0; N: 6.2%

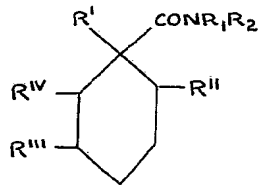
EXAMPLE XXIV

PREPARATION OF N,2-DIETHYL-CYCLOHEXANAMIDE

2-ethylcyclohexanoyl chloride was prepared in the usual way. The acid chloride was allowed to react with an excess of ethylamine in ether solution and the product was worked up as in Example XVIII to give N,2-diethylcyclohexanamide as a colourless liquid, bp. 84—94°/0.01 mm.

WHAT WE CLAIM IS:—

1. A manufactured product for application to or consumption by the human body comprising a physiologically active ingredient capable of stimulating the cold receptors of the nervous system of the body and a carrier therefor, said carrier constituting or providing a vehicle by means of which said ingredient may be brought into contact with the skin or other surface tissue of the body upon use of the said product, said carrier comprising a manufactured article or preparation into which the said ingredient is incorporated by admixture or impregnation and being other than a liquid or mixture of liquids which serve merely as solvent for the said ingredient and which contain no other ingredient, wherein said physiologically active ingredient is a cyclohexanamide of the formula



where

R′, R″, R‴ and R′ᵛ are each hydrogen or C_1—C_5 alkyl and together provide a total of from 1—8 carbon atoms, it being provided that at least two of R′, R″ and R‴ and R′ᵛ are hydrogen and that, when R′ and R′ᵛ are both hydrogen and R‴ is methyl, then R″ is methyl, ethyl, n-propyl or straight or branched chain butyl or amyl;

R_1 and R_2, when taken separately, each represent hydrogen, C_1—C_5 alkyl or C_1—C_8 hydroxylalkyl and together provide a total of no more than 8 carbon atoms with the proviso that when R_1 is hydrogen R_2 may also be alkylcarboxyalkyl of up to 6 carbon atoms; and

R_1 and R_2, when taken together, represent an alkylene group of up to 6 carbon atoms the ends of which group are attached to the amide nitrogen atom thereby to form a nitrogen heterocycle, the carbon atom chain of which may optionally be interrupted by oxygen.

2. A product according to claim 1, wherein the cold receptor stimulant is of the formula defined where one of R′ and R″ is hydrogen and the other is alkyl and one or both of R‴ and R′ᵛ is hydrogen.

3. A product according to claim 1 or 2, wherein the cold receptor stimulant is of the formula defined, where R′ is alkyl.

4. A product according to any one of claims 1—3, wherein said carrier is an edible preparation containing an edible base material and a flavourant or colourant.

5. A product of matter according to claim 4, wherein said carrier is a chewing gum.

6. A product according to any one of claims 1—3, wherein said carrier is an orally or topically administrable pharmaceutical preparation, comprising an orally or topically acceptable carrier and an orally or topically administrable pharmaceutically active ingredient.

7. A product according to any one of claims 1—3, wherein said carrier is a beverage containing a potable base material and a flavourant or colourant.

8. A product according to any one of claims 1—3, wherein said carrier is a dentifrice.

9. A product according to any one of claims 1—3, wherein said carrier is a mouthwash comprising an aqueous or aqueous/alcoholic solution of an orally acceptable antiseptic.

10. A product according to any one of claims 1—3, wherein said carrier is a mouth- for topical application to the body which comprises an aqueous or aqueous/alcoholic base and one or more of the following, a colourant, an odourant or an antiseptic.

11. A product according to any one of claims 1—3, wherein said carrier is an ointment, cream, or oil for topical application to the body.

12. A product according to any one of claims 1—3, wherein said carrier is a toilet soap or shampoo.

13. A product according to any one of claims 1—3, wherein said carrier is a shaving soap or foam.

14. A product according to any one of claims 1—3, wherein said carrier is a liquid impregnated cleansing tissue.

15. A product according to any one of claims 1—3, wherein said carrier is or contains tobacco.

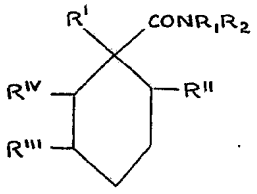
16. A product according to claim 15, wherein said carrier is a cigarette.

17. A product according to claim 16, wherein said carrier is a filter-tipped cigarette and wherein said ingredient is impregnated in the filter tip.

18. A product according to claim 1, being a product substantially as hereinbefore described in any one of the foregoing Examples.

19. A method of stimulating the cold receptors of the nervous system of the body, other than as part of a medical treatment, which comprises applying to the skin, or other surface tissue of the body, a compound of the formula defined in claim 1 or as modified by claim 2 or 3.

20. A compound of the formula



where R′, R″, R‴ and R^{v} are as defined in claim 1 except that together they provide a total of from 2—8 carbon atoms, R_1 when taken separately is hydrogen, C_1—C_5 alkyl or C_1—C_6 hydroxyalkyl, R_2 when taken separately, represents C_1—C_5 alkyl or C_1—C_6 hydroxyalkyl and together with R_1 provides a total of up to 8 carbon atoms, with the proviso that when R_1 is hydrogen, R_2 may also be alkylcarboxyalkyl of up to 6 carbon atoms; and when taken together R_1 and R_2 represent an alkylene group of up to 6 carbon atoms, the opposite ends of which group are attached to the amide nitrogen atom to form a nitrogen heterocycle, the carbon atom chain of which may be interrupted by oxygen.

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